

Title:

PRELIMINARY EXPERIENCE IN MAINTENANCE TREATMENT WITH INTRAVENOUS USTEKINUMAB AS A RESCUE FOR LOSS OF RESPONSE TO SUBCUTANEOUS DOSES

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Preliminary experience of maintenance treatment with intravenous ustekinumab as a rescue treatment for loss of response to subcutaneous doses

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ABSTRACT

It has been demonstrated that ustekinumab (UST) is effective as an induction and maintenance therapy in patients with Crohn's disease (CD). However, a significant number of patients experience an insufficient response or a secondary non-response. We report six cases from our center that underwent a rescue treatment by changing maintenance treatment to weight-adjusted intravenous UST, obtaining a subsequent clinical improvement.

Keywords: Ustekinumab. Crohn's disease. Loss of response. Rescue.

INTRODUCTION

Ustekinumab (UST) is a fully human immunoglobulin G monoclonal antibody that blocks the p40 subunit of interleukins (IL) 12 and 23. It is effective in inducing and maintaining remission in patients with Crohn's disease (CD). The recommended dosage for ustekinumab in the treatment of CD is an initial single intravenous induction dose based on body weight, followed by periodic subcutaneous doses of 90 mg (1). However, a significant number of patients are unresponsive or experience a secondary non-response (2).

It has been suggested that higher levels of UST may be associated with better clinical response rates (3) and there are published data on patients rescued with a reinduction treatment (4-6). Thus, it is also plausible to think that the administration of intravenous UST as a maintenance therapy may increase bioavailability and thus, combat a primary or secondary non-response.

Objective

The aim of the present study is to assess the efficacy of a rescue treatment with intravenous UST to induce remission in patients with moderate-severe CD, who present a partial response or loss of response to subcutaneous UST.

MATERIAL AND METHODS

After approval by our center's Ethics Committee, we present our preliminary experience in a series of six cases of CD, from an Inflammatory Bowel Disease Unit in a tertiary hospital. These cases presented a partial response or secondary non-response to subcutaneous UST treatment, based on clinical, biochemical or endoscopic criteria, and underwent rescue treatment with weight-adjusted intravenous UST.

Data was collected on gender, age, weight, smoking habit, disease phenotype (according to the Montreal classification), time of disease progression, previous biological treatments, previous surgeries, time from first dose of UST to the rescue dose, clinical and laboratory data prior to the rescue dose and at the eight-week follow-up. A descriptive statistical analysis was performed. Quantitative data were expressed as central tendency measures and inter-quartile ranges (IQRs), and qualitative variables were expressed as frequencies.

RESULTS

We present six female patients with moderate-severe CD; 83.3 % (5/6) had at least one previous surgery related to CD. The median time from onset was ten years (IQR 3.5-13.5). Ileal involvement occurred in 33.3 % (2/6) of cases, colonic in 16.7 % (1/6) and ileocolonic in 50 % (3/6). In addition, 83.3 % (5/6) of patients had associated perianal disease (Table 1).

One patient received UST following a failure of a single anti-TNF, the rest had failed on at least two biological treatments. The median time between initiation of UST and change from subcutaneous to intravenous and weight-adjusted maintenance dose was 5.5 months (IQR 2-10.25).

At the beginning of the rescue treatment with weight-adjusted intravenous dose, the mean value of Harvey's index was 7 (IQR 5-10), the mean value of C-reactive protein (CRP) and fecal calprotectin (FCP) was 1.4 mg/dl (IQR 0.975-1.85 mg/dl) and 1,040.0 mcg/g (IQR 248.25-1,939.25 mcg/g), respectively. In the eight-week follow-up after the first intravenous dose, the mean value of Harvey's index was 3.17 (IQR 2-4.25) and the mean CRP and FCP were 0.52 mg/dl (IQR 0.43-0.66 mg/dl) and 150.33 mcg/g (IQR 34-384 mcg/g), respectively. A decrease in the CRP value was observed in all cases, and a decrease in FCP in five patients after treatment with UST. There was an increase in the value of FCP in only one patient, which raised from 22 mcg/g to 66 mcg/g. It should be noted that there were no adverse effects recorded to date.

DISCUSSION

Six patients with moderate-severe CD and loss of response to several previous treatments showed an improvement in clinical response and a decrease in inflammation parameters with this rescue treatment. This is in accordance with data from previous publications (5-6). A modest increase in CPF was observed in just one patient. This case had ileal affectation, so this increase could be considered as less representative. In all patients, weight-adjusted intravenous UST was subsequently maintained. However, the long-term response has yet to be determined and this assessment was not included in this article. Future prospective studies are required to elucidate the best approach for optimizing UST treatment, as these preliminary data are retrospective, with a limited number of patients and a short follow-up period.

CONCLUSIONS

Treatment with UST is a great alternative for patients with CD who have not responded to anti-TNF treatment. However, there is still a percentage of patients with a partial response or loss of response to UST treatment. Weight-adjusted intravenous UST

rescue may be an option to consider in patients with a loss of response after subcutaneous maintenance treatment. However, more evidence is required as there are few publications on this subject.

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Table 1.

<i>Patient</i>	<i>Age (years)</i>	<i>Tobacco habit</i>	<i>Disease duration (years)</i>	<i>Time from UST start to rescue (months)</i>	<i>Montreal</i>	<i>Perianal disease</i>	<i>Prior biological therapies</i>	<i>Harvey pre- rescue</i>	<i>CRP (mg/dl) pre- rescue</i>	<i>FCP (mcg/g) pre- rescue</i>	<i>Harvey 8 weeks</i>	<i>CRP (mg/dl) 8 weeks</i>	<i>FCP (mcg/g) 8 weeks</i>
1	57	No	24	2	A2L3B2	Yes	1 st IFX 2 nd ADA	6	1.8	1,856	2	0.5	34
2	49	No	10	7	A2L1B2	Yes (complex)	IFX	7	1.1	323	4	0.5	220
3	50	Ex- smoker	4	10	A3L1B3	Yes (complex)	1 st ADA 2 nd IFX	5	0.6	24	3	0.5	66
4	31	No	10	11	A2L2B2	Yes (complex)	1 st ADA 2 nd IFX 3 rd VEDO	5	1.5	2,189	2	0.6	71
5	42	Yes	2	4	A2L3B1	No	1 st IFX	9	1.4	861	3	0.8	384

							2 nd ADA						
6	34	Yes	10	2	A2L3B1	Yes (complex)	1 st ADA 2 nd IFX	10	2.0	987	5	0.2	127

UST: ustekinumab; CRP: C-reactive protein; FCP: fecal calprotectin; ADA: adalimumab; IFX: infliximab; VEDO: vedolizumab.